

HIV strategically targets HIV-specific T cells

HIV enters cells by binding to CD4 and a chemokine coreceptor. As a result, the majority of HIV-infected cells in HIV-positive individuals are CD4⁺ T helper cells. CD4⁺ T cells recognise foreign peptide antigens, which are processed predominantly from extracellular proteins, and are bound to MHC class II molecules on the surface of antigen-presenting cells (APCs). CD4⁺ T cells perform a central role in the coordination of humoral and cellular immune responses. HIV infection is characterised by the progressive loss of CD4⁺ T cells. The gradual decline of these key immune orchestrators is followed, almost inevitably, by AIDS and death. It is known that CD4⁺ T-cell responses to HIV are generally lost early after infection (in the absence of therapeutic intervention), whereas responses specific for other antigens are preserved throughout the asymptomatic phase until the eventual collapse of the immune system. This led to the hypothesis that HIV might preferentially infect CD4⁺ T cells that respond to HIV antigens, resulting in their dysfunction or destruction.

The very nature of their specificity suggests that HIV-specific T cells are probably in prolonged close proximity to actively replicating HIV compared with other T cells. During early disease, rapid proliferation and the specific characteristics

of an activated phenotype, such as altered coreceptor expression, could render HIV-specific CD4⁺ T cells highly susceptible to infection as they progress from a naive to effector phenotype. A recent study provides direct evidence that HIV preferentially infects HIV-specific CD4⁺ T cells *in vivo*.

'...HIV-specific memory CD4⁺ T cells...contain significantly more viral DNA than CMV-specific CD4⁺ T cells or other memory CD4⁺ T cells'

Flow cytometry was used to sort HIV-specific, cytomegalovirus (CMV)-specific and unstimulated CD4⁺CD45RO⁺ memory cells from 12 HIV-infected individuals at different stages of infection by antigen-induced interferon (IFN)- γ production. Using quantitative PCR, Douek *et al.* [1] show that HIV-specific memory CD4⁺ T cells in these individuals contain significantly more viral DNA than CMV-specific CD4⁺ T cells ($p=0.0039$) or other memory CD4⁺ T cells ($p=0.0001$). Regardless of the stage of infection, HIV-specific CD4⁺ memory T cells were infected with HIV at a frequency of 2.1–5.3 times greater than memory CD4⁺ T cells with other specificities.

The implications of these findings are profound. First, preferential infection of HIV-specific CD4⁺ T cells by HIV probably explains the early loss of HIV-specific T-cell

help observed in the majority of infected individuals. This, in turn, will impair other effector arms of the HIV-specific immune response. Protecting HIV-specific T-cell help by early antiretroviral therapy and/or therapeutic vaccination could, therefore, enable the generation of effective immune responses and control of viraemia. Indeed, several recent studies support this idea. Second, the expanding pool of HIV-specific activated T helper cells during acute infection might provide the initial reservoir of cells for expansion of viral load and the establishment of chronic infection. Third, the preferential infection of HIV-specific CD4⁺ T cells by HIV might represent an elegant evolutionary mechanism that knocks out HIV-specific immunity without rendering the host immunocompromised to other pathogens during the long asymptomatic period of infection. This could prolong host–parasite coexistence, enabling HIV to replicate and disseminate over many years.

1 Douek, D.C. *et al.*, (2002) HIV preferentially infects HIV-specific CD4⁺ T cells. *Nature* 417, 95–98

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Unique role of the PI3-K δ isoform in immunity

There is increasing evidence of key roles for the class 1A phosphoinositide 3-kinases (PI-3-Ks) in the immune system. There are three class 1A catalytic subunits – p110 α , p110 β and p110 δ . Particular interest has focused on the δ isoform because this is expressed predominantly in leukocytes, suggesting a unique role in immune signaling. However, the specific role(s) for each of these catalytic isoforms in lymphocyte signaling is undetermined and it is not clear whether the isoforms have overlapping or distinct biological roles. A study by Okkenhaug *et al.* [1] has begun to peel away some of the layers of mystery surrounding the function of the individual p110 catalytic isoforms in lymphocytes.

This group used a new strategy to specifically address the role of the

p110 δ isoform. Instead of the deletion of a particular p110 isoform gene (previously shown to alter expression of other isoforms), they generated 'knock-in' mice that expressed a mutated p110 δ . This mutant was inactivated by point mutation

'...p110 δ has a role in the differentiation and/or survival of effector and memory T cells.'

(D910A, single amino-acid code) within the p110 δ catalytic domain. This approach prevented changes in the expression levels of the other PI3-K catalytic and regulatory subunits. The lipid kinase activity of p110 δ was completely abrogated in p110 δ mutated homozygous mice with no alteration in the kinase activities of p110 α or p110 β .

The p110 δ mutant mice exhibited several interesting defects in both B- and T-cell function. First, antigen-receptor signaling in B and T cells from p110 δ mutant mice was severely impaired compared with cells from wild-type mice. Thus, B-cell receptor (BCR)- and T-cell receptor (TCR)-stimulated phosphorylation of the PI3-K effector protein kinase B, and the mitogen-activated protein kinase ERK, as well as elevation of intracellular calcium, were all abrogated in accordance with the recognized role of PI3-K upstream of these signaling molecules. Also, consistent with the notion of p110 δ acting as a key mediator of BCR signaling, the p110 δ mutant mice had severe defects in B-cell development and differentiation, and proliferation of purified B cells by anti-IgM